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2,5-DIOXOIMIDAZOLIDIN-4-YLACETAMIDES AND ANALOGUES AS INHIBITORS OF METALLOPROTEMASE MMP12.

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

Metalloproteinases are a superfamily of proteinases (enzymes) whose numbers in recent years have increased dramatically. Based on structural and functional considerations these enzymes have been classified into families and subfamilies as described in N.M. Hooper (1994) FEBS Letters 354:1-6. Examples of metalloproteinases include the matrix metalloproteinases (MMPs) such as the collagenases (MMP1, MMP8, MMP13), the gelatinases (MMP2, MMP9), the stromelysins (MMP3, MMP10, MMP11), matrilysin (MMP7), metalloelastase (MMP12), enamelysin (MMP19), the MT-MMPs (MMP14, MMP15, MMP16, MMP17); the reprolysin or adamalysin or MDC family which includes the secretases and sheddases such as TNF converting enzymes (ADAM10 and TACE); the astacin family which include enzymes such as procollagen processing proteinase (PCP); and other metalloproteinases such as aggrecanase, the endothelin converting enzyme family and the angiotensin converting enzyme family.

Metalloproteinases are believed to be important in a plethora of physiological disease processes that involve tissue remodelling such as embryonic development, bone formation and uterine remodelling during menstruation. This is based on the ability of the metalloproteinases to cleave a broad range of matrix substrates such as collagen, proteoglycan and fibronectin. Metalloproteinases are also believed to be important in the processing, or secretion, of biological important cell mediators, such as tumour necrosis factor (TNF); and the post translational proteolysis processing, or shedding, of biologically important membrane proteins, such as the low affinity IgE receptor CD23 (for a more complete list see N. M. Hooper *et al.*, (1997) Biochem J. 321:265-279).

Metalloproteinases have been associated with many diseases or conditions. Inhibition of the activity of one or more metalloproteinases may well be of benefit in these diseases or

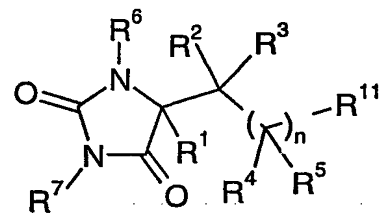
conditions, for example: various inflammatory and allergic diseases such as, inflammation of the joint (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis), inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease); in diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); Alzheimer's disease; extracellular matrix remodelling observed in cardiovascular diseases such as restenosis and atheroscelerosis; asthma; rhinitis; and chronic obstructive pulmonary diseases (COPD).

MMP12, also known as macrophage elastase or metalloelastase, was initially cloned in the mouse by Shapiro *et al* [1992, Journal of Biological Chemistry 267: 4664] and in man by the same group in 1995. MMP12 is preferentially expressed in activated macrophages, and has been shown to be secreted from alveolar macrophages from smokers [Shapiro *et al*, 1993, Journal of Biological Chemistry, 268: 23824] as well as in foam cells in atherosclerotic lesions [Matsumoto *et al*, 1998, Am J Pathol 153: 109]. A mouse model of COPD is based on challenge of mice with cigarette smoke for six months, two cigarettes a day six days a week. Wildtype mice developed pulmonary emphysema after this treatment. When MMP12 knock-out mice were tested in this model they developed no significant emphysema, strongly indicating that MMP12 is a key enzyme in the COPD pathogenesis. The role of MMPs such as MMP12 in COPD (emphysema and bronchitis) is discussed in Anderson and Shinagawa, 1999, Current Opinion in Anti-inflammatory and Immunomodulatory Investigational Drugs 1(1): 29-38. It was recently discovered that smoking increases macrophage infiltration and macrophage-derived MMP-12 expression

in human carotid artery plaques Kangavari [Matetzky S, Fishbein MC *et al.*, Circulation 102:(18), 36-39 Suppl. S, Oct 31, 2000].

A number of metalloproteinase inhibitors are known (see for example the reviews of MMP inhibitors by Beckett R.P. and Whittaker M., 1998, Exp. Opin. Ther. Patents, 8(3):259-282, and by Whittaker M. *et al*, 1999, Chemical Reviews 99(9):2735-2776).

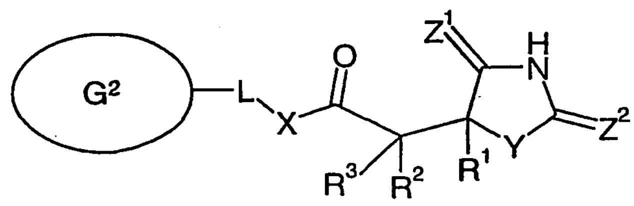
Published International Patent Application No. WO 02/096426 (Bristol- Myers Squibb Company) describes hydantoin derivatives of formula



in which the substituents R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^{11} are broadly defined. The derivatives are said, in general terms, to act as inhibitors of metalloproteinases, in particular TACE, MMPs and/or aggrecanase, although no data demonstrating biological activity is included in the application.

We have now discovered a new class of compounds that are potent and selective MMP12 inhibitors and have desirable activity profiles, in particular they are highly selective inhibitors for MMP12 relative to, for example, MMP14, MMP19 and TACE.

In accordance with the present invention, there is therefore provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof



(I)

wherein

X represents an oxygen atom or a group NR^4 or CH_2;

Y represents NH or N-methyl;

Z^1 and Z^2 each independently represent an oxygen or sulphur atom, provided that at least one of Z^1 and Z^2 represents an oxygen atom;

Either R^1 represents hydrogen or a group selected from C_1-C_6 alkyl and a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted with at least one substituent selected from halogen, hydroxyl, cyano, carboxyl, $-NR^5R^6$, $-CONR^7R^8$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylcarbonyl(oxy), $-S(O)_mC_1$-C_6 alkyl where m is 0, 1 or 2, C_1-C_6 alkylsulphonylamino, C_1-C_6 alkoxycarbonyl(amino), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with at least one substituent selected from halogen, hydroxyl, oxo (=O), carboxyl, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl and C_1-C_6 hydroxyalkyl,

R^2 represents hydrogen or C_1-C_6 alkyl, and

R^3 represents hydrogen or C_1-C_6 alkyl,

or

R^1 and R^2 together with the carbon atoms to which they are attached form a saturated 5- to 6-membered ring optionally comprising a ring heteroatom selected from nitrogen, oxygen and sulphur, and R^3 is as defined above,

or

R^2 and R^3 together with the carbon atom to which they are attached form a saturated 5- to 6-membered ring optionally comprising a ring heteroatom selected from nitrogen, oxygen and sulphur, and R^1 is as defined above;

R^4 represents hydrogen or C_1-C_6 alkyl;

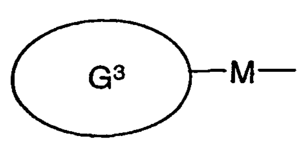
R^5, R^6, R^7 and R^8 each independently represent hydrogen or C_1-C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

L represents -$CH_2C(O)$- or -$C(O)CH_2$-, or

L represents a C_2-C_6 alkyl or C_2-C_6 alkynyl group optionally interrupted or terminated by at least one moiety selected from O, NH, S, SO, SO_2 and C(O), or L represents a C_3-C_6 cycloalkyl, methylC_3-C_6 cycloalkyl or C_3-C_6 cycloalkylmethyl group, each of the recited groups being optionally substituted with at least one substituent selected from hydroxyl, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy and C_1-C_4 haloalkoxy, or

L represents a C_3-C_4 alkylene chain, the ends of which are attached to adjacent ring carbon atoms in the 5- to 10-membered ring system of G^2 to form a ring;

G^2 represents a saturated or unsaturated 5- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted with at least one substituent selected from halogen, hydroxyl, cyano, nitro, C_1-C_6 alkyl (optionally substituted by one or more of cyano, halogen, hydroxyl and methoxy), C_2-C_6 alkenyl, C_1-C_6 alkoxy (optionally substituted by one or more halogen atoms), -$S(O)_nC_1$-C_6 alkyl where n is 0, 1 or 2, C_1-C_6 alkylcarbonyl(amino), C_1-C_6 alkylcarbonyloxy, phenyl, benzyloxy, $-NR^9R^{10}$ and a group of formula



(II);

R^9 and R^{10} each independently represent hydrogen or C_1-C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

M represents a bond or -O-, -S-, -C≡C-, -CH_2O- or -OCH_2-;

G^3 represents an unsaturated 5- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted with at least one substituent selected from halogen, hydroxyl, cyano, nitro, C_1-C_6 alkyl (optionally substituted by one or more of cyano, halogen, hydroxyl and methoxy), C_2-C_6 alkenyl, C_1-C_6 alkoxy (optionally substituted by one or more halogen atoms), -$S(O)_tC_1$-C_6 alkyl where t is 0, 1 or 2, C_1-C_6 alkylcarbonyl(amino), C_1-C_6 alkylcarbonyloxy, phenyl, benzyloxy and -$NR^{11}R^{12}$; and

R^{11} and R^{12} each independently represent hydrogen or C_1-C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy.

In the context of the present specification, unless otherwise stated, an alkyl, alkenyl or alkynyl substituent group or an alkyl moiety in a substituent group may be linear or branched. A haloalkyl or haloalkoxy substituent group will comprise at least one halogen atom, e.g. one, two, three or four halogen atoms. A hydroxyalkyl substituent may contain one or more hydroxyl groups but preferably contains one or two hydroxyl groups. When R^1 and R^2, or R^2 and R^3, form a ring, it should be understood that the ring may comprise up to one ring heteroatom only. In the definition of R^1, it should be noted that each of the saturated or unsaturated 3- to 10-membered ring system and the saturated or unsaturated 5- to 6-membered ring may have alicyclic or aromatic properties. The same comment applies to the saturated or unsaturated 5- to 10-membered ring system in the definition of G^2. An unsaturated ring system will be partially or fully unsaturated. When L represents a C_2-C_6 alkyl or C_2-C_6 alkynyl group optionally interrupted or terminated by more than one moiety (e.g. two moieties) selected from O, NH, S, SO, SO_2 and C(O), it may in some instances be possible for the two moieties to be adjacent to one another but otherwise the moieties will need to be separated by one or more carbon atoms. For example, whilst it is acceptable for C(O) or SO_2 and NH to be adjacent to one another, combinations such as NH-NH, NH-O, O-O, O-SO, O-SO_2, SO-SO, SO_2-SO_2 and so on are undesirable. The person skilled in the art will know which moieties may be placed next to one another.

In an embodiment of the invention, X represents an oxygen atom or a group NR^4 where R^4 represents hydrogen or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

In another embodiment of the invention, X represents NH or N-methyl. In a further embodiment, X represents NH.

In one embodiment, Z^1 and Z^2 both represent an oxygen atom.

In an embodiment of the invention, R^1 represents hydrogen or a group selected from C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) and a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each group being optionally substituted with at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, cyano, carboxyl, $-NR^5R^6$, $-CONR^7R^8$, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkylcarbonyl(oxy) (e.g. methylcarbonyl(oxy), ethylcarbonyl(oxy), n-propylcarbonyl(oxy), isopropylcarbonyl(oxy), n-butylcarbonyl(oxy), n-pentylcarbonyl(oxy) or n-hexylcarbonyl(oxy)), $-S(O)_mC_1$-C_6, preferably C_1-C_4, alkyl where m is 0, 1 or 2 (e.g. methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl or ethylsulphonyl), C_1-C_6, preferably C_1-C_4, alkylsulphonylamino (e.g. methylsulphonylamino, ethylsulphonylamino, n-propylsulphonylamino, isopropylsulphonylamino, n-butylsulphonylamino, n-pentylsulphonylamino or n-hexylsulphonylamino), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl(amino) (e.g. methoxycarbonyl(amino), ethoxycarbonyl(amino), n-propoxycarbonyl(amino) or

n-butoxycarbonyl(amino)), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, oxo, carboxyl, cyano, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl) and C_1-C_6, preferably C_1-C_4, hydroxyalkyl (e.g. $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ or $-CH(OH)CH_3$);

R^2 represents hydrogen or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl); and

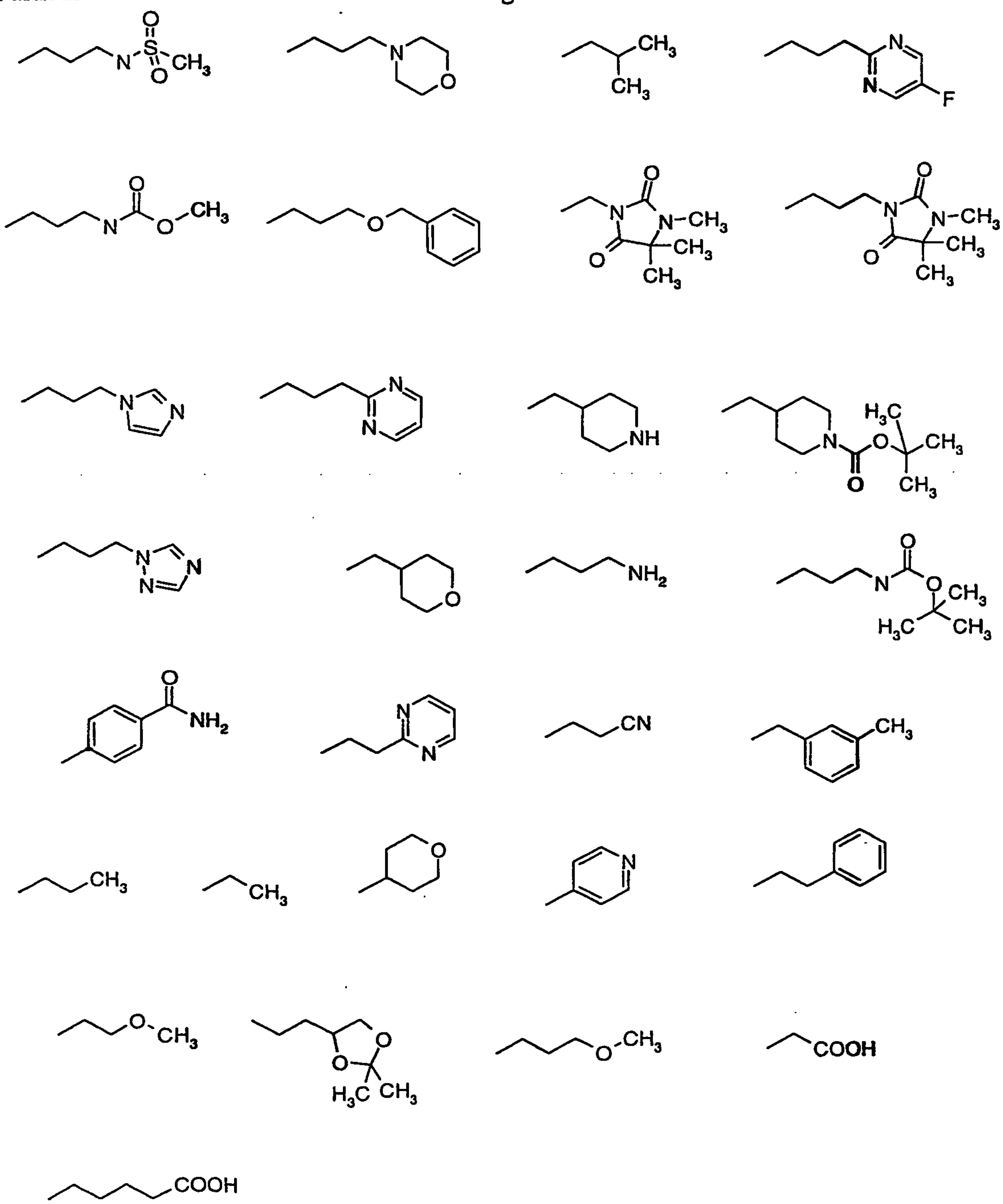
R^3 represents hydrogen or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

Examples of saturated or unsaturated 3- to 10-membered ring systems that may be used, which may be monocyclic or polycyclic (e.g. bicyclic) in which the two or more rings are fused, include one or more (in any combination) of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, cyclopentenyl, cyclohexenyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, diazabicyclo[2.2.1]hept-2-yl, naphthyl, benzofuranyl, benzothienyl, benzodioxolyl, quinolinyl, 2,3-dihydrobenzofuranyl, tetrahydropyranyl, pyrazolyl, pyrazinyl, thiazolidinyl, indanyl, thienyl, isoxazolyl, pyridazinyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, imidazolyl, pyrimidinyl, benzimidazolyl, triazolyl, tetrazolyl and pyridinyl. Preferred ring systems include phenyl, pyridinyl and tetrahydropyranyl.

Examples of saturated or unsaturated 5- to 6-membered ring substituents in R^1 include cyclopentyl, cyclohexyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiomorpholinyl, pyrazolyl, pyrazinyl, pyridazinyl, thiazolidinyl, thienyl, isoxazolyl, pyrimidinyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, imidazolyl,

triazolyl, tetrazolyl and pyridinyl. Preferred rings include morpholinyl, pyrimidinyl, phenyl, imidazolyl, piperidinyl, tetrahydropyranyl and triazolyl.

Particular values for R^1 include the following:



In another embodiment of the invention, R^1 represents hydrogen or a group selected from C_1-C_4 alkyl and a saturated or unsaturated 5- to 10-membered ring system which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each group being optionally substituted with at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen, hydroxyl, cyano, carboxyl, $-NR^5R^6$, $-CONR^7R^8$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylcarbonyl(oxy), $-S(O)_mC_1$-C_4 alkyl where m is 0, 1 or 2, C_1-C_4 alkylsulphonylamino, C_1-C_4 alkoxycarbonyl(amino), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen, hydroxyl, oxo, carboxyl, cyano, C_1-C_4 alkyl C_1-C_4 alkoxycarbonyl and C_1-C_4 hydroxyalkyl;

R^2 represents hydrogen or C_1-C_4 alkyl; and

R^3 represents hydrogen or C_1-C_4 alkyl.

In still another embodiment, R^1 represents hydrogen or C_1-C_4 alkyl, particularly methyl; R^2 represents hydrogen; and R^3 represents hydrogen.

Alternatively, R^1 and R^2 may together with the carbon atoms to which they are attached form a saturated 5- to 6-membered ring optionally comprising a ring heteroatom selected from nitrogen, oxygen and sulphur (e.g. cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, tetrahydrofuranyl or tetrahydrothiophenyl), and R^3 is as previously defined.

As a further alternative, R^2 and R^3 may together with the carbon atom to which they are attached form a saturated 5- to 6-membered ring optionally comprising a ring heteroatom selected from nitrogen, oxygen and sulphur (e.g. cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, tetrahydrofuranyl or tetrahydrothiophenyl), and R^1 is as previously defined.

R^5, R^6, R^7 and R^8 each independently represent hydrogen or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or iodine) and C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy).

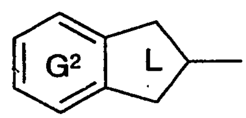
In an embodiment of the invention, R^5, R^6, R^7 and R^8 each independently represent hydrogen or C_1-C_6, preferably C_1-C_4, alkyl. In another embodiment, R^5, R^6, R^7 and R^8 each independently represent hydrogen.

L represents -$CH_2C(O)$- or -$C(O)CH_2$-, or

L represents a C_2-C_6, preferably C_2-C_4, alkyl or C_2-C_6, preferably C_2-C_4, alkynyl group optionally interrupted or terminated by at least one moiety (e.g. one or two moieties independently) selected from O, NH, S, SO, SO_2 and C(O) (for example, -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -C≡C-, -CH_2-C≡C-, -C≡C-CH_2-, -O-$(CH_2)_3$-NH-, -NH-$(CH_2)_3$-O-, -$CH(CH_3)$-, -$(CH_2)_2$-C(O)-, -C(O)-$(CH_2)_2$-, -$CH_2CH(CH_3)$-, -$CH(CH_3)CH_2$-, -$(CH_2)_2$-O-CH_2- or -CH_2-O-$(CH_2)_2$), or L represents a C_3-C_6 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), methylC_3-C_6 cycloalkyl (e.g. methylcyclopropyl) or C_3-C_6 cycloalkylmethyl (e.g. cyclopropylmethyl) group, each of the recited groups being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or iodine), C_1-C_4, preferably C_1-C_2, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl or t-butyl), C_1-C_4, preferably C_1-C_2, haloalkyl (e.g. trifluoromethyl or pentafluoroethyl), C_1-C_4, preferably C_1-C_2, alkoxy (e.g. methoxy or ethoxy) and C_1-C_4, preferably C_1-C_2, haloalkoxy (e.g. trifluoromethoxy)

(such as $-CH_2OCH(R)CH_2NH-$ or $-NHCH_2CH(R)OCH_2-$ where R represents methyl, hydroxyl or methoxy, $-CH(CH_3)-CH(OH)-$, $-CH(OH)-CH(CH_3)-$, $-CH_2CH(OH)-$, $-CH(OH)CH_2-$, $-CH_2CH(OCH_3)-$ or $-CH(OCH_3)CH_2-$), or

L represents a C_3-C_4 alkylene chain, the ends of which are attached to adjacent ring carbon atoms in the 5- to 10-membered ring system of G^2 to form a ring (for example, if G^2 represents an unsubstituted phenyl group and L represents a C_3 alkylene chain, G^2 and L together form a 2,3-dihydroinden-2-yl group having the structure:



In an embodiment of the invention, reading from left to right in formula (I),

L represents $-C(O)CH_2-$, or

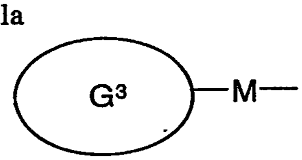
L represents C_2-C_4 alkyl optionally interrupted or terminated by an oxygen atom, cyclopropyl or cyclopropylmethyl, each of which is optionally substituted with one or two substituents independently selected from hydroxyl, halogen, methyl, trifluoromethyl, methoxy and trifluoromethoxy, or

L represents a C_3-C_4 alkylene chain, the ends of which are attached to adjacent ring carbon atoms in the 5- to 10-membered ring system of G^2 to form a ring.

In a further embodiment of the invention, L represents (reading from left to right in formula (I)) $-C(O)CH_2-$, $-(CH_2)_2-$, $-CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-CH(OH)-CH(CH_3)-$, $-CH(OH)CH_2-$, $-CH(OCH_3)CH_2-$, $-CH_2-O-(CH_2)_2$, cyclopropyl, cyclopropylmethyl, or L represents a C_3 alkylene chain, the ends of which are attached to adjacent ring carbon atoms in the 5- to 10-membered ring system of G^2 to form a ring.

G^2 represents a saturated or unsaturated 5- to 10-membered ring system which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted with at least one substituent (e.g. one, two, three or four substituents

independently) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, cyano, nitro, C_1-C_6, preferably C_1-C_4, alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl (optionally substituted by one or more, e.g. one, two or three, substituents independently selected from cyano, halogen such as chlorine, fluorine, bromine or iodine, hydroxyl and methoxy), C_2-C_6, preferably C_2-C_4, alkenyl (e.g. ethenyl, prop-1-enyl, prop-2-enyl, but-1-enyl, pent-1-enyl, hex-1-enyl or 2-methyl-pent-2-enyl), C_1-C_6, preferably C_1-C_4, alkoxy such as methoxy, ethoxy, n-propoxy or n-butoxy (optionally substituted by one or more, e.g. one, two or three, halogen atoms such as chlorine, fluorine, bromine or iodine), $-S(O)_nC_1$-C_6, preferably C_1-C_4, alkyl where n is 0, 1 or 2 (e.g. methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl or ethylsulphonyl), C_1-C_6, preferably C_1-C_4, alkylcarbonyl(amino) (e.g. methylcarbonyl(amino), ethylcarbonyl(amino), n-propylcarbonyl(amino), isopropylcarbonyl(amino), n-butylcarbonyl(amino), n-pentylcarbonyl(amino) or n-hexylcarbonyl(amino)), C_1-C_6, preferably C_1-C_4, alkylcarbonyloxy (e.g. methylcarbonyloxy, ethylcarbonyloxy, n-propylcarbonyloxy, isopropylcarbonyloxy, n-butylcarbonyloxy, n-pentylcarbonyloxy or n-hexylcarbonyloxy), phenyl, benzyloxy, $-NR^9R^{10}$ and a group of formula



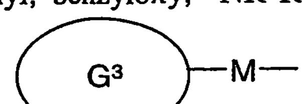
(II).

Examples of saturated or unsaturated 5- to 10-membered ring systems that may be used in G^2, which may be monocyclic or polycyclic (e.g. bicyclic) in which the two or more rings are fused, include one or more (in any combination) of cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, cyclopentenyl, cyclohexenyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, diazabicyclo[2.2.1]hept-2-yl, naphthyl, benzofuranyl, benzothienyl, benzodioxolyl, quinolinyl, 2,3-dihydrobenzofuranyl, tetrahydropyranyl, pyrazolyl, pyrazinyl, thiazolidinyl, indanyl, thienyl, isoxazolyl, pyridazinyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, imidazolyl, pyrimidinyl,

benzimidazolyl, triazolyl, tetrazolyl and pyridinyl. Preferred ring systems include phenyl, indolyl, thienyl and piperidinyl.

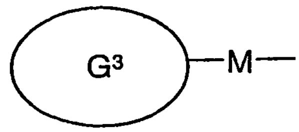
R^9 and R^{10} each independently represent hydrogen or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or iodine) and C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy).

In an embodiment of the invention, G^2 represents a saturated or unsaturated 5- to 9-membered ring system which may comprise one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted with one or two substituents independently selected from halogen, hydroxyl, cyano, nitro, C_1-C_4 alkyl (optionally substituted by one or more, e.g. one, two or three, substituents independently selected from cyano, halogen such as chlorine, fluorine, bromine or iodine, hydroxyl and methoxy), C_2-C_4 alkenyl, C_1-C_4 alkoxy (optionally substituted by one or more, e.g. one, two or three, halogen atoms such as chlorine, fluorine, bromine or iodine), -$S(O)_nC_1$-C_4 alkyl where n is 0, 1 or 2, C_1-C_4 alkylcarbonyl(amino), C_1-C_4 alkylcarbonyloxy, phenyl, benzyloxy, -NR^9R^{10} and a group of formula



(II).

In another embodiment, G^2 represents a saturated or unsaturated 5- to 9-membered ring system which may comprise one ring heteroatom selected from nitrogen and sulphur (e.g. phenyl, indolyl, thienyl or piperidinyl), the ring system being optionally substituted with one or two substituents independently selected from halogen, C_1-C_4 alkyl and a group of formula



(II).

In an embodiment of the invention, M represents a bond, -O- or -C≡C-. In a further embodiment, M represents a bond.

G^3 represents an unsaturated 5- to 10-membered ring system which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted with at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, cyano, nitro, C_1-C_6, preferably C_1-C_4, alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl (optionally substituted by one or more, e.g. one, two or three, substituents independently selected from cyano, halogen such as chlorine, fluorine, bromine or iodine, hydroxyl and methoxy), C_2-C_6, preferably C_2-C_4, alkenyl (e.g. ethenyl, prop-1-enyl, prop-2-enyl, but-1-enyl, pent-1-enyl, hex-1-enyl or 2-methyl-pent-2-enyl), C_1-C_6, preferably C_1-C_4, alkoxy such as methoxy, ethoxy, n-propoxy or n-butoxy (optionally substituted by one or more, e.g. one, two or three, halogen atoms such as chlorine, fluorine, bromine or iodine), $-S(O)_tC_1$-C_6, preferably C_1-C_4, alkyl where t is 0, 1 or 2 (e.g. methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl or ethylsulphonyl), C_1-C_6, preferably C_1-C_4, alkylcarbonyl(amino) (e.g. methylcarbonyl(amino), ethylcarbonyl(amino), n-propylcarbonyl(amino), isopropylcarbonyl(amino), n-butylcarbonyl(amino), n-pentylcarbonyl(amino) or n-hexylcarbonyl(amino)), C_1-C_6, preferably C_1-C_4, alkylcarbonyloxy (e.g. methylcarbonyloxy, ethylcarbonyloxy, n-propylcarbonyloxy, isopropylcarbonyloxy, n-butylcarbonyloxy, n-pentylcarbonyloxy or n-hexylcarbonyloxy), phenyl, benzyloxy and $-NR^{11}R^{12}$.

Examples of unsaturated 5- to 10-membered ring systems that may be used in G^3, which may be monocyclic or polycyclic (e.g. bicyclic) in which the two or more rings are fused, include one or more (in any combination) of cyclopentenyl, cyclohexenyl, phenyl, naphthyl, benzofuranyl, benzothienyl, benzodioxolyl, quinolinyl, 2,3-dihydrobenzofuranyl, pyrazolyl, pyrazinyl, thiazolidinyl, indanyl, thienyl, isoxazolyl, pyridazinyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, imidazolyl, pyrimidinyl, benzimidazolyl, triazolyl, tetrazolyl and pyridinyl. Preferred ring systems include phenyl, thienyl, naphthyl, benzofuranyl, benzothienyl, pyridinyl, pyrrolyl, furanyl, benzodioxolyl, quinolinyl and 2,3-dihydrobenzofuranyl.

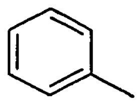
R^{11} and R^{12} each independently represent hydrogen or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or iodine) and C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy).

In one embodiment, G^3 represents an unsaturated 5- to 10-membered ring system which may comprise one or two ring heteroatoms independently selected from nitrogen, oxygen and sulphur (e.g. phenyl, thienyl, naphthyl, benzofuranyl, benzothienyl, pyridinyl, pyrrolyl, furanyl, benzodioxolyl, quinolinyl and 2,3-dihydrobenzofuranyl), the ring system being optionally substituted with one or two substituents independently selected from halogen, hydroxyl, cyano, nitro, C_1-C_4 alkyl (optionally substituted by one or more, e.g. one, two or three, substituents independently selected from cyano, halogen such as chlorine, fluorine, bromine or iodine, hydroxyl and methoxy), C_2-C_4 alkenyl, C_1-C_4 alkoxy (optionally substituted by one or more, e.g. one, two or three, halogen atoms such as chlorine, fluorine, bromine or iodine), $-S(O)_tC_1$-C_4 alkyl where t is 0, 1 or 2, C_1-C_4 alkylcarbonyl(amino), C_1-C_4 alkylcarbonyloxy, phenyl, benzyloxy and $-NR^{11}R^{12}$

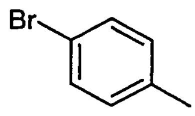
In another embodiment, G^3 represents an unsaturated 5- to 10-membered ring system which may comprise one or two ring heteroatoms independently selected from nitrogen, oxygen and sulphur (e.g. phenyl, thienyl, naphthyl, benzofuranyl, benzothienyl, pyridinyl, pyrrolyl, furanyl, benzodioxolyl, quinolinyl and 2,3-dihydrobenzofuranyl), the ring system being optionally substituted with one or two substituents independently selected from halogen, cyano, nitro, C_1-C_4 alkyl (optionally substituted by one or more, e.g. one, two or three, substituents independently selected from cyano and halogen), C_1-C_4 alkoxy (optionally substituted by one or more, e.g. one, two or three, halogen atoms), C_1-C_4 alkylthio, C_1-C_4 alkylcarbonyl(amino), phenyl and benzyloxy.

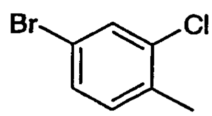
In still another embodiment, G^3 represents an unsaturated 5- to 10-membered ring system which may comprise one or two ring heteroatoms independently selected from nitrogen, oxygen and sulphur (e.g. phenyl, thienyl, naphthyl, benzofuranyl, benzothienyl, pyridinyl, pyrrolyl, furanyl, benzodioxolyl, quinolinyl and 2,3-dihydrobenzofuranyl), the ring system being optionally substituted with one or two substituents independently selected from fluorine, chlorine, cyano, nitro, methyl, cyanomethyl, trifluoromethyl, methoxy, trifluoromethoxy, methylthio, methylcarbonyl (acetyl), methylcarbonylamino (acetylamino), phenyl and benzyloxy.

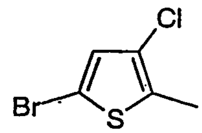
Particular values for G^2 include the following:

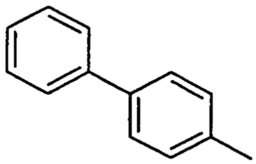


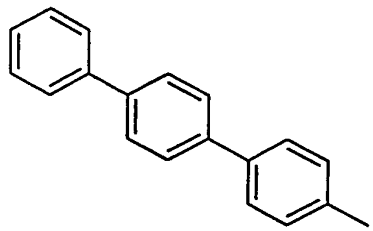
(phenyl)

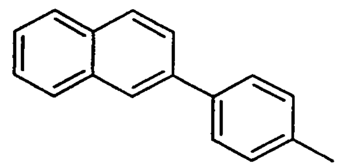


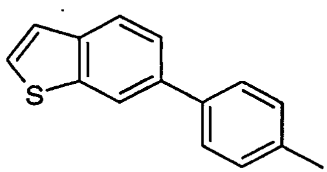


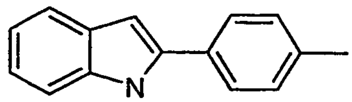


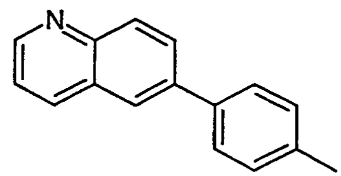


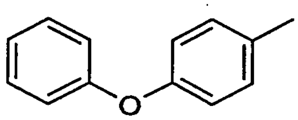


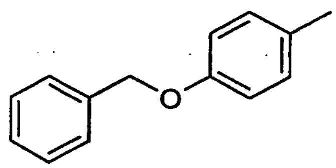


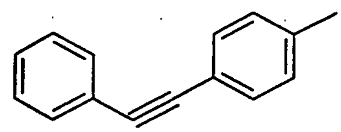


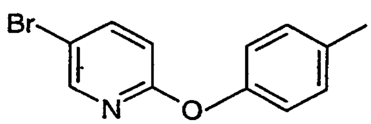












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In an embodiment of the invention:

X represents –NH- or -N(CH_3)-;

Y represents NH;

Z^1 and Z^2 both represent an oxygen atom;

R^1 represents hydrogen or methyl;

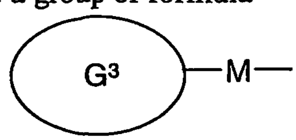
R^2 represents hydrogen;

R^3 represents hydrogen;

L represents $-C(O)CH_2-$, $-(CH_2)_2-$, $-CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-CH(OH)-CH(CH_3)-$, $-CH(OH)CH_2-$, $-CH(OCH_3)CH_2-$, $-CH_2-O-(CH_2)_2$, cyclopropyl, cyclopropylmethyl, or

L represents a C_3 alkylene chain, the ends of which are attached to adjacent ring carbon atoms in the 5- to 9-membered ring system of G^2 to form a ring;

G^2 represents represents a saturated or unsaturated 5- to 9-membered ring system which may comprise one ring heteroatom selected from nitrogen and sulphur, the ring system being optionally substituted with one or two substituents independently selected from halogen, C_1-C_4 alkyl and a group of formula



(II);

M represents a bond, -O- or -C≡C-; and

G^3 represents an unsaturated 5- to 10-membered ring system which may comprise one or two ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted with one or two substituents independently selected from fluorine, chlorine, cyano, nitro, methyl, cyanomethyl, trifluoromethyl, methoxy, trifluoromethoxy, methylthio, methylcarbonyl, methylcarbonylamino, phenyl and benzyloxy.

Examples of compounds of the invention include:

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-fluoro-biphenyl-4-yl)-ethyl]-acetamide,

N-[2-(4'-Cyano-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-phenyl-cyclopropyl)-acetamide,

N-[2-(4-Chlorophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-(2-Biphenyl-4-yl-ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(7-methyl-1H-indol-3-yl)ethyl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-phenoxyphenyl)ethyl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-fluorophenyl)ethyl]-acetamide,

N-[2-(4-Bromophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(2,4-Dichlorophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(3'-Chloro-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Benzyloxy-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-thiophen-3-yl-phenyl)ethyl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-thiophen-2-yl-phenyl)ethyl]-acetamide,

N-[2-(4'-Chloro-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-methylsulfanyl-biphenyl-4-yl)ethyl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-nitro-biphenyl-4-yl)ethyl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-methyl-biphenyl-4-yl)ethyl]-acetamide,

N-[2-(3'-Acetylamino-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-naphthalen-2-yl-phenyl)ethyl]-acetamide,

N-[2-(3',5'-Dichloro-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-methyl-biphenyl-4-yl)ethyl]-acetamide,

N-[2-(4-Benzofuran-2-yl-phenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-methoxy-biphenyl-4-yl)ethyl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-[1,1';4',1"]terphenyl-4-ylethyl)-acetamide,

N-[2-(4'-Acetyl-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4-Benzo[b]thiophen-2-yl-phenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Cyanomethyl-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-pyridin-3-yl-phenyl)ethyl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{2-[4-(1H-pyrrol-2-yl)phenyl]ethyl}-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-furan-3-yl-phenyl)ethyl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-furan-2-yl-phenyl)ethyl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-thiophen-2-yl-ethyl)-acetamide,

N-[2-(4-tert-Butylphenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4-Chlorophenyl)-1-methylethyl]-2-(2,5-dioxoimidazolidin-4-yl)acetamide,

N-{[1-(4-Chlorophenyl)cyclopropyl]methyl}-2-(2,5-dioxoimidazolidin-4-yl)acetamide,

N-2,3-Dihydro-1H-inden-2-yl-2-(2,5-dioxoimidazolidin-4-yl)acetamide,

N-[2-(4-Chlorophenyl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide,

N-[2-(4-Chlorophenyl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide,

N-[2-(4'-Cyano-1,1'-biphenyl-4-yl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide,

N-[2-(4'-Fluoro-1,1'-biphenyl-4-yl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-fluoro-1,1'-biphenyl-4-yl)propyl]-acetamide,

N-[(1*S*,2*R*)-2-(4'-Methoxybiphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[(1*S*,2*R*)-2-(4'-Cyanobiphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[(1*S*,2*R*)-2-(4'-Acetylbiphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-{(1*S*,2*R*)-2-[4'-(Acetylamino)biphenyl-4-yl]cyclopropyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Cyanobiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-methoxybiphenyl-4-yl)ethyl]-acetamide,

N-[2-(4'-Cyano-3'-methylbiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-methyl-*N*-(2-phenylethyl)-acetamide,

N-[1-(4-Chlorophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-acetamide,

N-{2-[4-(1,3-Benzodioxol-5-yl)phenyl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-methoxybiphenyl-4-yl)propyl]-acetamide,

N-{2-[3'-(Acetylamino)biphenyl-4-yl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(3'-Acetylbiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Acetylbiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-{2-[4-(1-Benzothien-2-yl)phenyl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(3'-Cyanobiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Cyanobiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-fluoro-3'-methylbiphenyl-4-yl)propyl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{2-[3'-(methylthio)biphenyl-4-yl]propyl}-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{2-[4-(6-methoxypyridin-3-yl)phenyl]propyl}-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-methoxy-3'-methylbiphenyl-4-yl)propyl]-acetamide,

N-{2-[4-(2,3-Dihydro-1-benzofuran-5-yl)phenyl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{2-[3'-(trifluoromethoxy)biphenyl-4-yl]propyl}-acetamide,

N-[2-(3',4'-Dimethoxybiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-quinolin-3-ylphenyl)propyl]-acetamide,

N-[2-(4'-Cyano-3'-methylbiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(1,3-Benzodioxol-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[5-(3-methoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-acetamide,

N-{5-[3-(Acetylamino)phenyl]-2,3-dihydro-1H-inden-2-yl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(3-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(4-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(1-Benzothien-2-yl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(3-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(4-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[5-(4-fluoro-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{5-[3-(methylthio)phenyl]-2,3-dihydro-1H-inden-2-yl}-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[5-(6-methoxypyridin-3-yl)-2,3-dihydro-1H-inden-2-yl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[5-(4-methoxy-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-acetamide,

N-[5-(2,3-Dihydro-1-benzofuran-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)acetamide,

N-[5-(3,4-Dimethoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Fluorobiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-{2-[4-(1,3-Benzodioxol-5-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(3'-Methoxybiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-{2-[4-(1-Benzothien-2-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(3'-Cyanobiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Fluoro-3'-methylbiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-*N*-{2-[3'-(methylthio)biphenyl-4-yl]propyl}-acetamide,

N-{2-[4-(6-Methoxypyridin-3-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Methoxy-3'-methylbiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-{2-[4-(2,3-Dihydro-1-benzofuran-5-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-*N*-{2-[3'-(trifluoromethoxy)biphenyl-4-yl]propyl}-acetamide,

N-[2-(3',4'-Dimethoxybiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-*N*-[2-(4-quinolin-3-ylphenyl)propyl]-acetamide,

N-[5-(4-Fluorophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(1,3-Benzodioxol-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(3-Methoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-{5-[3-(Acetylamino)phenyl]-2,3-dihydro-1H-inden-2-yl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(3-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(4-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(1-Benzothien-2-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(3-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(4-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(4-Fluoro-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-*N*-{5-[3-(methylthio)phenyl]-2,3-dihydro-1H-inden-2-yl}-acetamide,

N-[5-(6-Methoxypyridin-3-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(4-Methoxy-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(2,3-Dihydro-1-benzofuran-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-*N*-{5-[3-(trifluoromethoxy)phenyl]-2,3-dihydro-1H-inden-2-yl}-acetamide,

N-[5-(3,4-Dimethoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(4-Cyano-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-{4-[4 (trifluoromethyl)phenoxy]phenyl}ethyl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{2-[4-(4-methoxyphenoxy)phenyl]ethyl}-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-{4-[4-(trifluoromethoxy)phenoxy]phenyl}ethyl)-acetamide,

N-{2-[4-(4-Chlorophenoxy)phenyl]ethyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-{2-[4-(4-Acetylphenoxy)phenyl]ethyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{2-[4-(pyridin-3-yloxy)phenyl]ethyl}-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-{4-[(6-methoxypyridin-3-yl)oxy]phenyl}ethyl)-acetamide,

N-{2-[4-(4-Cyanophenoxy)phenyl]ethyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{2-[4-(4-methylphenoxy)phenyl]ethyl}-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{2-[4-(4-fluorophenoxy)phenyl]ethyl}-acetamide,

N-(2-Biphenyl-4-yl-2-hydroxy-ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(1,1'-Biphenyl-4-yl)-2-methoxyethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(1,1'-Biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-N-methylacetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-phenylethynyl-piperidin-1-yl)ethyl]-acetamide,

N-{2-[(4-Bromobenzyl)oxy]ethyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(1,1'-Biphenyl-4-yl)-2-oxoethyl (2,5-dioxoimidazolidin-4-yl)acetate,

and pharmaceutically acceptable salts and solvates thereof.

It will be appreciated that the particular substituents and number of substituents in the compounds of the invention are selected so as to avoid sterically undesirable combinations.

Each exemplified compound represents a particular and independent aspect of the invention.

It will be appreciated that the compounds according to the invention may contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centres (chiral centres) in compounds according to the invention can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof. Racemates may be separated into individual optically active forms using known procedures (cf. Advanced Organic Chemistry: 3rd Edition: author J March, p104-107) including for example the formation of diastereomeric derivatives having convenient optically active auxiliary species followed by separation and then cleavage of the auxiliary species.

Where optically active centres exist in the compounds of the invention, we disclose all individual optically active forms and combinations of these as individual specific embodiments of the invention, as well as their corresponding racemates.

Where tautomers exist in the compounds of the invention, we disclose all individual tautomeric forms and combinations of these as individual specific embodiments of the invention.

The compounds of the invention may be provided as pharmaceutically acceptable salts or solvates. These include acid addition salts such as hydrochloride, hydrobromide, citrate, tosylate and maleate salts and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine. Examples of solvates include hydrates.

The compounds of formula (I) have activity as pharmaceuticals. As previously outlined the compounds of the invention are metalloproteinase inhibitors, in particular they are inhibitors of MMP12 and may be used in the treatment of diseases or conditions mediated

by MMP12 such as asthma, rhinitis, chronic obstructive pulmonary diseases (COPD), arthritis (such as rheumatoid arthritis and osteoarthritis), atherosclerosis and restenosis, cancer, invasion and metastasis, diseases involving tissue destruction, loosening of hip joint replacements, periodontal disease, fibrotic disease, infarction and heart disease, liver and renal fibrosis, endometriosis, diseases related to the weakening of the extracellular matrix, heart failure, aortic aneurysms, CNS related diseases such as Alzheimer's disease and Multiple Sclerosis (MS), and hematological disorders.

The compounds of the invention show a favourable selectivity profile. Whilst we do not wish to be bound by theoretical considerations, the compounds of the invention are believed to show selective inhibition for any one of the above indications relative to any MMP1 inhibitory activity, by way of non-limiting example they may show 100-1000 fold selectivity over any MMP1 inhibitory activity.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention further provides a method of treating a disease or condition mediated by MMP12 which comprises administering to a patient a therapeutically effective amount of a

compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as hereinbefore defined.

The invention also provides a method of treating an obstructive airways disease (e.g. asthma or COPD) which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I)/salt/solvate (active ingredient) may be in the range from 0.001 mg/kg to 75 mg/kg, in particular from 0.5 mg/kg to 30 mg/kg. This daily dose may be given in divided doses as necessary. Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as

hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

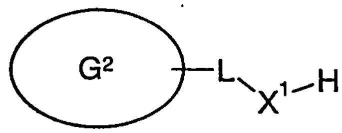
The pharmaceutical compositions of this invention may be administered in standard manner for the disease or condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal adminstration or by inhalation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more diseases or conditions referred to hereinabove such as "Symbicort" (trade mark) product.

Preparation of the compounds of the invention

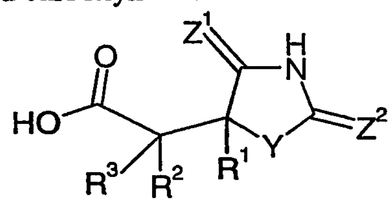
The present invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined above which comprises,

(a) when X represents an oxygen atom or a group NR^4, reacting a compound of formula



(III)

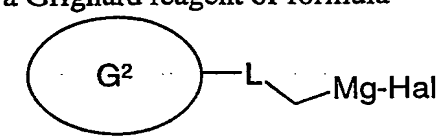
wherein X^1 represents an oxygen atom or a group NR^4 and L, G^2 and R^4 are as defined in formula (I), with an activated carboxylic acid of formula



(IV)

wherein Y, Z^1, Z^2, R^1, R^2 and R^3 are as defined in formula (I); or

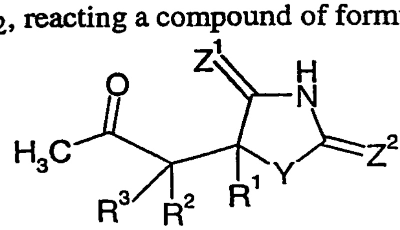
(b) when X represents CH_2, reacting an activated carboxylic acid of formula (IV) as defined in (a) above with methoxymethylamine or a salt thereof (e.g. hydrochloride salt) followed by reaction with a Grignard reagent of formula



(V)

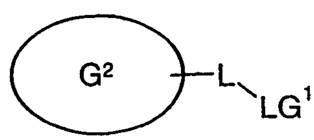
wherein Hal represents a halogen atom such as chlorine or bromine and L and G^2 are as defined in formula (I); or

(c) when X represents CH_2, reacting a compound of formula



(VI)

wherein Y, Z^1, Z^2, R^1, R^2 and R^3 are as defined in formula (I), with a compound of formula



(VII)

wherein LG^1 represents a leaving group such as halogen or sulphonate (e.g. methylsulphonate or toluenesulphonate) and L and G^2 are as defined in formula (I), in the presence of a strong base (e.g. sodium hydride or lithium diisopropylamide);

and optionally after (a), (b) or (c) forming a pharmaceutically acceptable salt or solvate.

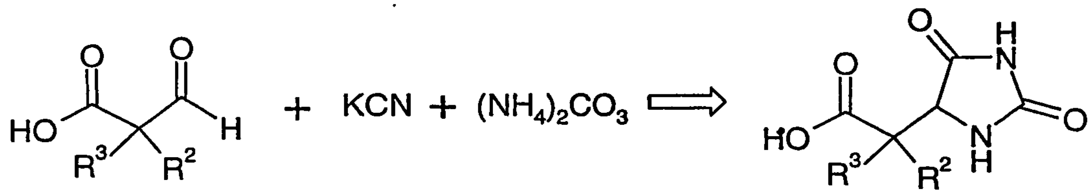
In process (a), the reaction between the compounds of formulae (III) and (IV) represents a simple amide or ester coupling well known to those skilled in the art. The carboxylic acid of formula (IV) must be activated in some way, for example as the acid halide, anhydride, acyl urea or acyl derivative of N-hydroxysuccinimide. For a general description of the preparation of amides and esters see, for example, Carey, F.A. and Sundberg, J., Advanced Organic Chemistry, 3rd Edition, pp 144-152, 1990.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of the invention may involve, at various stages, the addition and removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

Compounds of formulae (III), (IV), (V), (VI) and (VII) are either commercially available, are known in the literature or may be prepared using known techniques.

For example, compounds of formula (IV) in which R^1 represents a hydrogen atom, Y represents NH and Z^1 and Z^2 both represent oxygen may be prepared accoding to the reaction scheme below:



Intermediate 1

Alternatively, compounds of formula (IV) in which R^1 represents a hydrogen atom, Y represents NH, Z^1 represents sulphur and Z^2 represent oxygen may be prepared by reacting Intermediate 1 above with thiocarbamic acid (H_2N-C(S)-OH) and sodium cyanide in the presence of a solvent mixture of ethanol and water, e.g. as described in *J. Chem. Soc.*, 1959, page 396.

Other methods are available for preparing compounds of formula (IV). For example, a wide range of α-amino acids are useful as synthons to dioxo-imidazolidines and oxo-thioxo-imidazolidines. It is well known that salts of cyanic acid, urea, or thiocyanic acid together with an ammonium salt react with α-amino acids to form these heterocycles (Anteunis, M.J.O.; Spiessens, L.; Witte, M. De; Callens, R.; Reyniers, *Bull. Soc. Chim. Belg.*, EN, 96, 6, 1987, 459-466; Dakin; *Am. Chem. J.*, 44, 1910, 49; Haurowitz et al., *J. Biol. Chem.*, 224, 1957).

Several suitable dioxo-imidazolidine and oxo-thioxo-imidazolidine acids are commercially available or are described in the literature as indicated below (unless otherwise stated, the numbers in brackets are CAS registry numbers):

(2,5-Dioxo-imidazolidin-4-yl)-acetic acid *(5427-26-9, 26184-52-1, 26184-53-2, 67337-71-7);*

(3-Methyl-2,5-dioxo-imidazolidin-4-yl)-acetic acid *(26972-46-3);*

5-Oxo-2-thioxo-imidazolidin-4-yl)-acetic acid *(41679-36-1, 61160-00-7);*

(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)-acetic acid *(62985-01-7);*

(4-Methyl-2,5-dioxo-imidazolidin-4-yl)-acetic acid *(beilstein registry number 145446);*

4-Imidazolidineacetic acid, 4-(hydroxymethyl)-2,5-dioxo-, (4R)- (9CI) *(391870-39-6);*

4-Imidazolidineacetic acid, 4-(4-chlorophenyl)-2,5-dioxo- (9CI) *(250352-11-5);*

4-Imidazolidineacetic acid, α-methyl-2,5-dioxo- (9CI) *(184681-52-5);*

1,3-Diazaspiro[4.4]nonane-6-carboxylic acid, 2,4-dioxo-, cis- (9CI) *(147676-21-9);*

1,3-Diazaspiro[4.5]decane-6-carboxylic acid, 2,4-dioxo- (7CI, 8CI) *(947-10-4);*

1,3-Diazaspiro[4.4]nonane-6-carboxylic acid, 2-oxo-4-thioxo- (9CI) *(197315-95-0);*

4-Imidazolidineacetic acid, 5-oxo-2-thioxo- (9CI) *(41679-36-1);*

4,4-Imidazolidinediacetic acid, 2,5-dioxo- (8CI, 9CI) *(5624-17-9);* and

4-Imidazolidineacetic acid, 4-hydroxy-2,5-dioxo- (9CI) *(78703-76-1).*

The present invention will now be further explained by reference to the following illustrative examples.

General procedures

^{1}HNMR and ^{13}CNMR were recorded on a Varian ^{unity} *Inova* 400 MHz or a Varian *Mercury*-VX 300 MHz instrument. The central peaks of chloroform-*d* (δ_H 7.27ppm), dimethylsulfoxide-d_6 (δ_H 2.50 ppm) or methanol-d_4 (δ_H 3.31 ppm) where used as internal references. Low-resolution mass spectra were obtained on an Agilent 100 LC-MS system equipped with an APCI ionisation chamber. Column chromatography was carried out using silica gel (0.063-0.2 mm) (Merck). Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were laboratory grade and used as received.

Abbreviations:

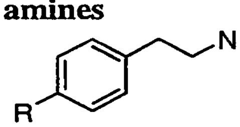
NMP:	1-methyl-2-pyrollidinone
TFA:	trifluoroacetic acid
HOBT:	1-hydroxybenzotriazole

$PdCl_2$ (dppf):	bis(diphenylphosphino)ferrocene-palladium(II)chloride dichloromethane complex
THF:	tetrahydrofuran
BOC:	*tert*-butoxycarbonyl
EtOH:	ethanol
EtOAc:	ethyl acetate
TLC:	thin layer chromatography
DMSO:	dimethyl sulphoxide
PEG:	polyethylene glycol

Examples

A. General procedure for preparation of 2-(2,5-Dioxo-imidazolidin-4-yl)-acetamides

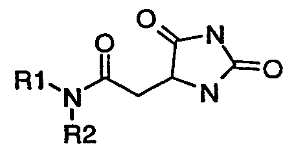
I. Preparation of non-commercial amines



2-(4-Bromo-phenyl)-ethylamine (2mmol, 400mg) was dissolved in 4mL THF (dry, mol sieves) and di-tert-butyl dicarbonate (1.2eq 2.4mmol 520mg) was added slowly.
The reaction mixture was stirred in room temperature for 1 hour before it was diluted with 100mL ethyl acetate and washed with 100mL sat. $NaHCO_3$/aq. The organic phase was dried over Na_2SO_4, filtrated and evaporated to dryness. The BOC-protected amine was dissolved in a mixture of 10mL toluene, 2.5mL ethanol and 2.5mL 2M Na_2CO_3/aq. $PdCl_2$(dppf) (0.03eq, 50mg) was added together with a corresponding boronic acid (1.05eq, 2.1mmol). The solution was degassed with nitrogen and the vessel was sealed before it was stirred overnight at 80°C. The reaction mixture was diluted with 50mL toluene and 50mL water. After mixing, the organic layer was transferred directly on to a silica column and purified by chromatography (toluene- ethylacetate). To remove the protecting group the compound was stirred in a mixture of 5mL conc. HCl in 10mL THF

for 30 min. The solution was neutralised with 1M NaOH/aq and extracted with dichloromethane (2x). The combined organic layers was dried over Na_2SO_4, filtrated and evaporated to dryness. The amines were used in the amide synthesis without any further purification.

II. Coupling of amines to 5 hydantoin acetic acid:- amide synthesis



600µL of a 0.15M solution in NMP of 5-hydantoin acetic acid was mixed with 98mg of polystyrene-bound carbodiimide resin (loading 1.28mmol/g). 340µL of a 0.3M solution of HOBT in NMP was added to the mixture and vortexed for 10 minutes before 200µL of a 0.3M solution in NMP of the corresponding amine was added. The reaction mixtures were vortexed overnight at room temperature in sealed vessels. Resin was removed by filtration and the solution was evaporated to dryness. The products were purified on semiprep-HPLC C_{18}-column (H_2O:CH_3CN, 0.1% TFA buffer, gradient 10% to 95% CH_3CN, 10 min).

The following 2-(2,5-Dioxo-imidazolidin-4-yl)-acetamides were prepared according to the general procedure A outlined above.

<u>**Example 1**</u>

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4'-fluoro-biphenyl-4-yl)-ethyl]-acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.56 (1H, s); 8.07 (1H, t); 7.71-.7.65 (2H, m); 7.59-.7.55 (2H, m); 7.32-.7.24 (4H, m); 4.23-4.19 (1H, m); 3.35-3.26 (2H, m); 2.75 (2H , t) 2.56-2.37(2H, m)

APCI-MS m/z: 356.4 [MH$^+$]

<u>**Example 2**</u>

N-[2-(4'-Cyano-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.56 (1H, s); 8.07 (1H, t); 7.92-.7.84 (4H, m); 7.79 (1H, s); 7.69 (2H, d); 7.35 (2H, d); 4.21(1H, t); 3.37-3.27 (2H, m); 2.78 (2H , t) 2.57-2.36(2H, m)

APCI-MS m/z: 363.4 [MH^+]

Example 3

2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-phenyl-cyclopropyl)-acetamide

APCI-MS m/z: 274.3 [MH^+]

Example 4

N-[2-(4-Chlorophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 296.3 [MH^+]

Example 5

N-(2-Biphenyl-4-yl-ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 338.4 [MH^+]

Example 6

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(7-methyl-1H-indol-3-yl)ethyl]-acetamide

APCI-MS m/z: 315.3 [MH^+]

Example 7

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-phenoxyphenyl)ethyl]-acetamide

APCI-MS m/z: 354.4 [MH^+]

Example 8

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-fluorophenyl)ethyl]-acetamide

APCI-MS m/z: 280.3 [MH^+]

Example 9

N-[2-(4-Bromophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 340.3 ; 342.3 [MH$^+$]

Example 10

N-[2-(2,4-Dichlorophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 330.3 ; 332.3[MH$^+$]

Example 11

N-[2-(3'-Chloro-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 372.4 [MH$^+$]

Example 12

N-[2-(4'-Benzyloxy-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 444.5 [MH$^+$]

Example 13

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-thiophen-3-yl-phenyl)ethyl]-acetamide

APCI-MS m/z: 344.3 [MH$^+$]

Example 14

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-thiophen-2-yl-phenyl)ethyl]-acetamide

APCI-MS m/z: 344.3 [MH$^+$]

Example 15

N-[2-(4'-Chloro-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 372.3 [MH$^+$]

Example 16

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4'-methylsulfanyl-biphenyl-4-yl)ethyl]-acetamide

APCI-MS m/z: 384.4 [MH^+]

Example 17

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(3'-nitro-biphenyl-4-yl)ethyl]-acetamide

APCI-MS m/z: 383.4 [MH^+]

Example 18

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4'-methyl-biphenyl-4-yl)ethyl]-acetamide

APCI-MS m/z: 352.4 [MH^+]

Example 19

N-[2-(3'-Acetylamino-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 395.4 [MH^+]

Example 20

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-naphthalen-2-yl-phenyl)ethyl]-acetamide

APCI-MS m/z: 388.4 [MH^+]

Example 21

N-[2-(3',5'-Dichloro-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 406.3 ; 408.4 [MH^+]

Example 22

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(3'-methyl-biphenyl-4-yl)ethyl]-acetamide

APCI-MS m/z: 352.4 [MH^+]

Example 23

N-[2-(4-Benzofuran-2-yl-phenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 378.4 [MH^+]

Example 24

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(3'-methoxy-biphenyl-4-yl)ethyl]-acetamide

APCI-MS m/z: 368.3 [MH^+]

Example 25

2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-[1,1';4',1"]terphenyl-4-ylethyl)-acetamide

APCI-MS m/z: 414.4 [MH^+]

Example 26

N-[2-(4'-Acetyl-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 380.4 [MH^+]

Example 27

N-[2-(4-Benzo[b]thiophen-2-yl-phenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 394.4 [MH^+]

Example 28

N-[2-(4'-Cyanomethyl-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 377.4 [MH^+]

Example 29

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-pyridin-3-yl-phenyl)ethyl]-acetamide

APCI-MS m/z: 339.4 [MH^+]

Example 30

2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[4-(1H-pyrrol-2-yl)phenyl]ethyl}-acetamide

APCI-MS m/z: 327.4 [MH^+]

Example 31

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-furan-3-yl-phenyl)ethyl]-acetamide

APCI-MS m/z: 328.4 [MH^+]

Example 32

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-furan-2-yl-phenyl)ethyl]-acetamide

APCI-MS m/z: 328.4 [MH^+]

Example 33

2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-thiophen-2-yl-ethyl)-acetamide

APCI-MS m/z: 268.3 [MH^+]

Example 34

N-[2-(4-tert-Butylphenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 318.4 [MH^+]

Example 35

N-[2-(4-Chlorophenyl)-1-methylethyl]-2-(2,5-dioxoimidazolidin-4-yl)acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.55(1H, d); 7.88 (1H, dd); 7.76 (1H, d); 7.33-7.31 (2H, m); 7.21-7.19 (2H, m); 4.19-4.16 (1H, m); 3.94-3.88 (1H, m); 2.77-2.32 (4H, m); 0.99 (3H, dd)

APCI-MS m/z: 310.3 [MH^+]

Example 36

N-{[1-(4-Chlorophenyl)cyclopropyl]methyl}-2-(2,5-dioxoimidazolidin-4-yl)acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.53(1H, d); 7.95 (1H, t); 7.73 (1H, s); 7.33-7.25 (4H, m); 4.18-4.15 (1H, m); 3.39-3.22 (2H, m); 2.54-2.37 (2H, m); 0.90-0.88 (2H, m); 0.76-0.73 (2H, m)

APCI-MS m/z: 322.3 [MH$^+$]

Example 37

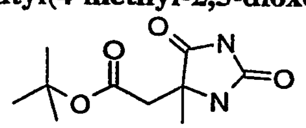
N-2,3-Dihydro-1H-inden-2-yl-2-(2,5-dioxoimidazolidin-4-yl)acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.54(1H, d); 8.24 (1H, d); 7.82 (1H, s); 7.22-7.20(2H, m); 7.16-7.13 (2H , m); 4.47-4.42 (1H, m); 4.22-4.19(1H, m); 3.19-3.12(2H, m); 2.80-2.72 (2H, m); 2.54-2.36 (2H, m)

APCI-MS m/z: 274.2 [MH$^+$]

B. General procedure for preparation of (4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamides

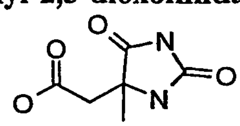
I. tert-butyl(4-methyl-2,5-dioxoimidazolidin-4-yl)acetate



Tert-butyl acetoacetate (200mg; 1.3mmol), KCN (165mg; 2.5mmol) and $(NH_4)_2CO_3$ (605mg; 6.3mmol) was suspended in EtOH (2mL) and H_2O (2mL) in a sealed tube. The mixture was heated to 85-90 °C and a solution was obtained, the heating was continued over night. The resulting slightly yellow solution was allowed to cool to roomtemperature and a precipitate was formed. The mixture was neutralised with 5%$NaHSO_4$ (aq) and diluted with H_2O (30mL). The slurry was extracted with EtOAc (2x50 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated to give the title compound as a colourless solid. Obtained 210 mg (73% yield).

^{1}H-NMR(DMSO-D6): δ 10.58 (1H, s), 7.91 (1H, s), 2.76+2.39 (1H each, ABq), 1.35 (9H, s), 1.23 (3H, s) ppm.

II. (4-methyl-2,5-dioxoimidazolidin-4-yl)-acetic acid



Deprotection afforded the title compound.

The following (4-methyl-2,5-dioxoimidazolidin-4-yl)acetamides were prepared by coupling of the appropiate amine to (4-methyl-2,5-dioxoimidazolidin-4-yl)-acetic acid by the general procedure A above.

<u>**Example 38**</u>

N-[2-(4-Chlorophenyl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.42(1H, s); 7.94(1H, t); 7.35(1H, s); 7.35-7.31 (2H, m); 7.24-7.21 (2H, m) ; 3.21 (2H, q); 2,67 (2H, dd); 2.53-2.36 (2H, m); 1.21 (3H, s)

APCI-MS m/z: 310.3 [MH$^+$]

<u>**Example 39**</u>

N-[2-(4-Chlorophenyl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.42 (1H,m); 7.89-7.86 (1H, m); 7.65-7.64 (1H, m); 7.35-7.32 (2H, m); 7.24-7.22 (2H, m); 3.19-3.09 (2H, m); 2.87-2.77 (1H, m); 2.53-2.37 (2H, m); 1.19 (3H, d); 1.14 (3H, d)

APCI-MS m/z: 324.4 [MH$^+$]

<u>**Example 40**</u>

N-[2-(4'-Cyano-1,1'-biphenyl-4-yl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide

APCI-MS m/z: 377.3 [MH$^+$]

Example 41

N-[2-(4'-Fluoro-1,1'-biphenyl-4-yl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.42 (1H,s); 7.99 (1H, t); 7.97-7.65 (3H, m); 7.56 (2H, d); 7.30-7.24 (4H, m); 3.28-3.23 (2H, m); 2.73-2.70 (2H, m); 2.54-2.39 (2H, m); 1.22 (3H, s)

APCI-MS m/z: 370.4 [MH^+]

Example 42

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-fluoro-1,1'-biphenyl-4-yl)propyl]-acetamide

a) 2-(4-Bromo-phenyl)-propylamine

2-Phenyl-propylamine (1g, 7.4mmol) was dissolved in n-hexane (30mL) and HBr/aq (5 drops) together with ZnBr on silica (1.75mmol/g, 1g). Br_2 (14.8 mmol, 900μL) was slowly added and the slurry was stirred over night. The slurry was diluted with ethyl acetate (300mL) and washed with 2M Na_2CO_3 (300mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness. Purification and separation of regioisomers was done on semi prep-HPLC C_{18}-column (H_2O:CH_3CN, 1% NH_4OAc buffer, gradient 10% to 60% CH_3CN, 30 min). Yield 23%

b) [2-(4-Bromo-phenyl)-propyl]-carbamic acid tert-butyl ester

2-(4-Bromo-phenyl)-propylamine (18.7 mmol, 4g) was dissolved in 50mL THF (dry, mol sieves) and di-tert-butyl dicarbonate (1.2eq 23mmol 5g) was added slowly. The reaction mixture was stirred at room temperature for 1 hour before it was diluted with 300mL ethyl acetate and washed with 300mL sat. $NaHCO_3$/aq. The organic phase was dried over Na_2SO_4, filtrated and evaporated to dryness.

c) [2-(4'-Fluoro-biphenyl-4-yl)-propyl]-carbamic acid tert-butyl ester

The BOC-protected amine obtained in b) above was dissolved in a mixture of 10mL toluene, 2.5mL ethanol and 2.5mL 2M Na_2CO_3/aq. $PdCl_2$(dppf) (0.03eq, 50mg) and 4-fluorobenzeneboronic acid (1.05eq, 2.1mmol) were added. The solution was degassed with nitrogen and the vessel was sealed before it was stirred overnight at 80°C. The reaction mixture was diluted with 50mL toluene and 50mL water. After mixing, the organic layer was transferred directly on to a silica column and purified by chromatography (toluene- ethyl acetate).

d) 2-(4'-Fluoro-biphenyl-4-yl)-propylamine

To remove the protecting group the compound obtained in c) above was stirred in a mixture of 5mL conc. HCl in 10mL THF for 30 min. The solution was neutralised with 1M NaOH/aq and extracted with dichloromethane (2x). The combined organic layers was dried over Na_2SO_4, filtrated and evaporated to dryness.

e) 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-fluoro-1,1'-biphenyl-4-yl)propyl]-acetamide

600μL of a 0.15M solution in NMP of 5-hydantoin acetic acid was mixed with 98mg of polystyrene-bound carbodiimide resin (loading 1.28mmol/g). 340μL of a 0.3M solution of HOBT in NMP was added to the mixture and vortexed for 10 minutes before 200μL of a 0.3M solution in NMP of 2-(4'-fluoro-biphenyl-4-yl)-propylamine was added. The reaction mixture was vortexed overnight at room temperature in a sealed vessel. Resin was removed by filtration and the solution was evaporated to dryness. The product was purified on semi prep-HPLC C_{18}-column (H_2O:CH_3CN, 0.1% TFA buffer, gradient 10% to 95% CH_3CN, 10 min).

^{1}H NMR (400MHz,DMSO-d_6): δ 10.55 (s, 1H), 8.00 (s, 1H), 7.76 (s, 1H), 7.68 (dd, J = 8.7, 5.5 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.32 - 7.25 (m, 4H), 4.22 - 4.17 (m, 1H), 3.23 (dd, J = 20.7, 6.3 Hz, 2H), 2.92 (q, J = 7.0 Hz, 1H), 2.57 - 2.35 (m, 2H), 1.21 (d, J = 7.1 Hz, 3H).

APCI-MS m/z: 370.2 [MH^+]

The following compounds were prepared according to methods analogous to Example 42 above.

Example 43

N-[(1S,2R)-2-(4'-Methoxybiphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.44 (d, J = 7.6 Hz, 1H), 8.18 (dd, J = 6.8, 4.3 Hz, 1H), 7.73 (s, 1H), 7.54 (d, J = 8.9 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H), 7.13 (dd, J = 8.3, 2.8 Hz, 2H), 6.99 (d, J = 8.9 Hz, 2H), 3.77 (s, 3H), 2.79 - 2.73 (m, 1H), 2.56 - 2.46 (m, 1H), 2.37 (d, J = 15.2 Hz, 1H), 1.90 (dt, J = 6.1, 3.1 Hz, 1H), 1.23 (s, 3H), 1.17 - 1.09 (m, 2H).

APCI-MS m/z: 394.3 [MH$^+$]

Example 44

N-[(1S,2R)-2-(4'-Cyanobiphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 389.3 [MH$^+$]

Example 45

N-[(1S,2R)-2-(4'-Acetylbiphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.44 (d, J = 8.3 Hz, 1H), 8.20 (dd, J = 7.3, 4.3 Hz, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.5 Hz, 2H), 7.73 (s, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.21 (dd, J = 8.3, 3.1 Hz, 2H), 2.80 (dd, J = 7.4, 4.0 Hz, 1H), 2.59 (s, 3H), 2.56 - 2.35 (m, 2H), 1.95 (tq, J = 6.2, 3.2 Hz, 1H), 1.23 (s, 3H), 1.22 - 1.13 (m, 2H).

APCI-MS m/z: 406.3[MH$^+$]

Example 46

***N*-{(1*S*,2*R*)-2-[4'-(Acetylamino)biphenyl-4-yl]cyclopropyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide**

APCI-MS m/z: 421.3 [MH$^+$]

Example 47

***N*-[2-(4'-Cyanobiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide**

^{1}H NMR (400MHz,DMSO-d_6): δ 10.43 (s, 1H), 7.95 - 7.85 (m, 5H), 7.67 (dd, *J* = 14.2, 8.5 Hz, 3H), 7.36 (dd, *J* = 8.3, 1.7 Hz, 2H), 1.19 (s, 3H), 1.21 (d, *J* = 3.9 Hz, 3H), 3.20 (sextet, *J* = 6.8 Hz, 2H), 2.94 - 2.87 (m, H), 2.54 - 2.39 (m, 2H).

APCI-MS m/z: 391.3 [MH$^+$]

Example 48

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-methoxybiphenyl-4-yl)ethyl]-acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.56 (s, 1H), 8.07 (t, *J* = 5.5 Hz,1H), 7.80 (s, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 2.0 Hz, 1H), 6.91 (dd, *J* = 8.1, 2.3 Hz, 1H), 4.24 - 4.20 (m, 1H), 3.82 (s, 3H), 3.34 - 3.26 (m, 2H), 2.75 (t, *J* = 7.3 Hz, 2H), 2.57 - 2.37 (m, 2H).

APCI-MS m/z: 368.2 [MH$^+$]

Example 49

***N*-[2-(4'-Cyano-3'-methylbiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide**

^{1}H NMR (400MHz,DMSO-d_6): δ 10.41 (s, 1H), 7.92 (t, *J* = 5.6 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.77 (s, 1H), 7.69 - 7.62 (m, 4H), 7.34 (dd, *J* = 8.3, 1.7 Hz, 2H), 3.18 (t, *J* = 6.5 Hz, 2H), 2.89 (dd, *J* = 6.9, 2.6 Hz, 1H), 1.18 (s, 3H), 1.20 (d, *J* = 4.1 Hz, 3H), 2.53 (s, 3H), 2.51 - 2.38 (m, 2H).

APCI-MS m/z: 405.3[MH$^+$]

Example 50

2-(2,5-Dioxoimidazolidin-4-yl)-N-methyl-N-(2-phenylethyl)-acetamide

APCI-MS m/z: 276.2 [MH^+]

Example 51

N-[1-(4-Chlorophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 296.1 [MH^+]

Example 52

2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-hydroxy-1-methyl-2-phenylethyl)-acetamide

APCI-MS m/z: 292.3[MH^+]

Example 53

N-{2-[4-(1,3-Benzodioxol-5-yl)phenyl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 396.5 [MH^+]

Example 54

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(3'-methoxybiphenyl-4-yl)propyl]-acetamide

APCI-MS m/z: 382.4 [MH^+]

Example 55

N-{2-[3'-(Acetylamino)biphenyl-4-yl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 409.5 [MH^+]

Example 56

N-[2-(3'-Acetylbiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 394.4 [MH$^+$]

Example 57

N-[2-(4'-Acetylbiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 394.5 [MH$^+$]

Example 58

N-{2-[4-(1-Benzothien-2-yl)phenyl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 408.4 [MH$^+$]

Example 59

N-[2-(3'-Cyanobiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 377.4 [MH$^+$]

Example 60

N-[2-(4'-Cyanobiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 377.4 [MH$^+$]

Example 61

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4'-fluoro-3'-methylbiphenyl-4-yl)propyl]-acetamide

APCI-MS m/z: 384.4 [MH$^+$]

Example 62

2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[3'-(methylthio)biphenyl-4-yl]propyl}-acetamide

APCI-MS m/z: 398.4 [MH$^+$]

Example 63

2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[4-(6-methoxypyridin-3-yl)phenyl]propyl}-acetamide

APCI-MS m/z: 383.4 [MH^+]

Example 64

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4'-methoxy-3'-methylbiphenyl-4-yl)propyl]-acetamide

APCI-MS m/z: 396.5 [MH^+]

Example 65

N-{2-[4-(2,3-Dihydro-1-benzofuran-5-yl)phenyl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 394.5 [MH^+]

Example 66

2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[3'-(trifluoromethoxy)biphenyl-4-yl]propyl}-acetamide

APCI-MS m/z: 436.5 [MH^+]

Example 67

N-[2-(3',4'-Dimethoxybiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 412.5 [MH^+]

Example 68

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-quinolin-3-ylphenyl)propyl]-acetamide

APCI-MS m/z: 403.5 [MH^+]

Example 69

N-[2-(4'-Cyano-3'-methylbiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 391.5 [MH^+]

Example 70

N-[5-(1,3-Benzodioxol-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 394.4 [MH^+]

Example 71

2-(2,5-Dioxoimidazolidin-4-yl)-N-[5-(3-methoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-acetamide

APCI-MS m/z: 380.4 [MH^+]

Example 72

N-{5-[3-(Acetylamino)phenyl]-2,3-dihydro-1H-inden-2-yl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 407.5 [MH^+]

Example 73

N-[5-(3-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 392.4 [MH^+]

Example 74

N-[5-(4-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 392.5 [MH^+]

Example 75

N-[5-(1-Benzothien-2-yl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 406.4 [MH^+]

Example 76

N-[5-(3-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 375.4 [MH^+]

Example 77

N-[5-(4-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 375.4 [MH^+]

Example 78

2-(2,5-Dioxoimidazolidin-4-yl)-N-[5-(4-fluoro-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-acetamide

APCI-MS m/z: 382.4 [MH^+]

Example 79

2-(2,5-Dioxoimidazolidin-4-yl)-N-{5-[3-(methylthio)phenyl]-2,3-dihydro-1H-inden-2-yl}-acetamide

APCI-MS m/z: 396.4 [MH^+]

Example 80

2-(2,5-Dioxoimidazolidin-4-yl)-N-[5-(6-methoxypyridin-3-yl)-2,3-dihydro-1H-inden-2-yl]-acetamide

APCI-MS m/z: 381.4 [MH^+]

Example 81

2-(2,5-Dioxoimidazolidin-4-yl)-N-[5-(4-methoxy-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-acetamide

APCI-MS m/z: 394.5 [MH^+]

Example 82

N-[5-(2,3-Dihydro-1-benzofuran-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)acetamide

APCI-MS m/z: 392.4 [MH^+]

Example 83

N-[5-(3,4-Dimethoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 410.5 [MH^+]

Example 84

N-[2-(4'-Fluorobiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 384.5 [MH^+]

Example 85

N-{2-[4-(1,3-Benzodioxol-5-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 410.5 [MH^+]

<u>Example 86</u>

N-[2-(3'-Methoxybiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 396.5 [MH+]

<u>Example 87</u>

N-{2-[4-(1-Benzothien-2-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 422.5 [MH+]

<u>Example 88</u>

N-[2-(3'-Cyanobiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 391.5 [MH+]

<u>Example 89</u>

N-[2-(4'-Fluoro-3'-methylbiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 398.5 [MH+]

<u>Example 90</u>

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-N-{2-[3'-(methylthio)biphenyl-4-yl]propyl}-acetamide

APCI-MS m/z: 412.5 [MH+]

<u>Example 91</u>

N-{2-[4-(6-Methoxypyridin-3-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 397.5 [MH+]

Example 92

N-[2-(4'-Methoxy-3'-methylbiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 410.5 [MH^+]

Example 93

N-{2-[4-(2,3-Dihydro-1-benzofuran-5-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 408.5 [MH^+]

Example 94

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-N-{2-[3'-(trifluoromethoxy)biphenyl-4-yl]propyl}-acetamide

APCI-MS m/z: 450.5 [MH^+]

Example 95

N-[2-(3',4'-Dimethoxybiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 426.5[MH^+]

Example 96

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-N-[2-(4-quinolin-3-ylphenyl)propyl]-acetamide

APCI-MS m/z: 417.5 [MH^+]

Example 97

N-[5-(4-Fluorophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 382.5 [MH^+]

Example 98

N-[5-(1,3-Benzodioxol-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 408.5 [MH^+]

Example 99

N-[5-(3-Methoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 394.5 [MH^+]

Example 100

N-{5-[3-(Acetylamino)phenyl]-2,3-dihydro-1H-inden-2-yl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 421.5 [MH^+]

Example 101

N-[5-(3-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 406.5 [MH^+]

Example 102

N-[5-(4-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 406.5 [MH^+]

Example 103

N-[5-(1-Benzothien-2-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 420.5 [MH^+]

Example 104

N-[5-(3-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 389.5 [MH^+]

Example 105

N-[5-(4-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 389.5 [MH^+]

Example 106

N-[5-(4-Fluoro-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 396.5 [MH^+]

Example 107

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-N-{5-[3-(methylthio)phenyl]-2,3-dihydro-1H-inden-2-yl}-acetamide

APCI-MS m/z: 410.5 [MH^+]

Example 108

N-[5-(6-Methoxypyridin-3-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 395.5 [MH^+]

Example 109

N-[5-(4-Methoxy-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 408.5 [MH^+]

Example 110

N-[5-(2,3-Dihydro-1-benzofuran-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 406.5 [MH^+]

Example 111

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-N-{5-[3-(trifluoromethoxy)phenyl]-2,3-dihydro-1H-inden-2-yl}-acetamide

APCI-MS m/z: 448.5 [MH^+]

Example 112

N-[5-(3,4-Dimethoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 424.5 [MH^+]

Example 113

N-[5-(4-Cyano-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 403.5 [MH^+]

Example 114

2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-{4-[4 (trifluoromethyl)phenoxy]phenyl}ethyl)-acetamide

a) [2-(4-Hydroxy-phenyl)-ethyl]-carbamic acid tert-butyl ester

2-(4-Hydroxyphenyl)-ethylamine (36.5mmol, 5g) was dissolved in 100mL THF (dry, mol sieves) and di-tert-butyl dicarbonate (1.2eq 43.8mmol, 9.5g) was added slowly. The reaction mixture was stirred at room temperature for 1 hour before it was diluted with 700mL ethyl acetate and washed with 500mL sat. $NaHCO_3$/aq. The organic phase was dried over Na_2SO_4, filtrated and evaporated to dryness.

b) {2-[4-(4-Trifluoromethyl-phenoxy)-phenyl]-ethyl}-carbamic acid tert-butyl ester

0.5mmol of the BOC-protected amine obtained in a) above was dissolved in dichloromethane (5mL) together with copper(II)acetate (0.5mmol, 90mg), powdered 4Å mol sieves (app. 100mg) and 4-(trifluoromethyl)benzeneboronic acid (1mmol). After stirring the reaction mixture overnight at room temperature the slurry was filtered and purified by flash chromatography.

c) 2-[4-(4-Trifluoromethyl-phenoxy)-phenyl]-ethylamine

The BOC-group was removed by stirring the compound obtained in b) above in hydrochloric acid/THF (0.5mL conc. HCl /1.5mL THF) for 2 hours at room temperature before it was made basic by adding 10.5mL 1M NaOH/aq. The free amine was extracted with 3x10mL dichloromethane that was dried over Na_2SO_4, filtrated and evaporated to dryness. Yield 0.32 mmol (62%).

d) 2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-{4-[4 (trifluoromethyl)phenoxy]-phenyl}ethyl)-acetamide

The title compound was prepared by a method analogous to that described in Example 42e).

^{1}H NMR (400MHz,DMSO-d_6): δ 10.55 (s, 1H), 8.05 (t, J = 5.6 Hz, 1H), 7.79 (s, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.08 (dd, J = 20.1, 8.5 Hz, 4H), 4.20 (dd, J = 6.2, 4.8 Hz, 1H), 3.29 (q, J = 6.8 Hz, 2H), 2.73 (t, J = 7.3 Hz, 2H), 2.57 - 2.36 (m, 2H).

APCI-MS m/z: 422.3 [MH^+]

The following compounds were prepared according to methods analogous to Example 114 above.

Example 115

2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[4-(4-methoxyphenoxy)phenyl]ethyl}-acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.54 (s, 1H), 8.01 (t, J = 5.5 Hz, 1H), 7.77 (s, 1H), 7.16 (d, J = 8.6 Hz, 2H), 6.97 - 6.91 (m, 4H), 6.83 (d, J = 8.5 Hz, 2H), 4.18 (dd, J = 6.2, 4.6 Hz, 1H), 3.72 (s, 3H), 3.22 (q, J = 6.8 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H), 2.55 - 2.33 (m, 2H).

APCI-MS m/z: 384.3 [MH^+]

Example 116

2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-{4-[4-(trifluoromethoxy)phenoxy]phenyl}ethyl)-acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.55 (s, 1H), 8.04 (t, J = 5.5 Hz, 1H), 7.79 (s, 1H), 7.37 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.07 (td, J = 6.4, 4.0 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 4.20 (dd, J = 6.1, 4.7 Hz, 1H), 3.27 (q, J = 6.8 Hz, 2H), 2.71 (t, J = 7.4 Hz, 2H), 2.57 - 2.35 (m, 2H).

APCI-MS m/z: 438.3 [MH^+]

Example 117

N-{2-[4-(4-Chlorophenoxy)phenyl]ethyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.55 (s, 1H), 8.04 (t, J = 5.5 Hz, 1H), 7.79 (s, 1H), 7.41 (dd, J = 12.4, 3.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 7.01 - 6.95 (m, 4H), 4.20 (dd, J = 6.1, 4.7 Hz, 1H), 3.26 (q, J = 6.8 Hz, 2H), 2.70 (t, J = 7.4 Hz, 2H), 2.57 - 2.34 (m, 2H).

APCI-MS m/z: 388.3 [MH^+]

Example 118

N-{2-[4-(4-Acetylphenoxy)phenyl]ethyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.55 (s, 1H), 8.05 (t, J = 5.7 Hz, 1H), 7.97 (d, J = 8.9 Hz, 2H), 7.80 (s, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.04 (t, J = 8.8 Hz, 4H), 4.22 - 4.19 (m, 1H), 3.33 - 3.24 (m, 2H), 2.73 (t, J = 7.2 Hz, 2H), 2.58 - 2.35 (m, 5H).

APCI-MS m/z: 396.3 [MH$^+$]

Example 119

2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[4-(pyridin-3-yloxy)phenyl]ethyl}-acetamide

APCI-MS m/z: 355.3 [MH$^+$]

Example 120

2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-{4-[(6-methoxypyridin-3-yl)oxy]phenyl}ethyl)-acetamide

APCI-MS m/z: 385.1 [MH$^+$]

Example 121

N-{2-[4-(4-Cyanophenoxy)phenyl]ethyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.57 (s, 1H), 8.05 (t, J = 5.5 Hz, 1H), 7.81 (d, J = 8.9 Hz, 2H), 7.79 (s, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.8 Hz, 4H), 4.20 (dd, J = 6.1, 4.8 Hz, 1H), 3.28 (q, J = 6.7 Hz, 2H), 2.73 (t, J = 7.3 Hz, 2H), 2.56 - 2.36 (m, 2H).

APCI-MS m/z: 379.3 [MH$^+$]

Example 122

2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[4-(4-methylphenoxy)phenyl]ethyl}-acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.55 (s, 1H), 8.03 (t, J = 5.5 Hz, 1H), 7.79 (s, 1H), 7.21 - 7.16 (m, 4H), 6.89 (d, J = 8.2 Hz, 4H), 4.20 (dd, J = 6.0, 4.5 Hz, 1H), 3.25 (q, J = 6.8 Hz, 2H), 2.68 (t, J = 7.4 Hz, 2H), 2.56 - 2.35 (m, 2H), 2.28 (s, 3H).

APCI-MS m/z: 368.3 [MH$^+$]

Example 123

2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[4-(4-fluorophenoxy)phenyl]ethyl}-acetamide

^{1}H NMR (400MHz,DMSO-d_6): δ 10.53 (s, 1H), 8.02 (t, J = 5.5 Hz, 1H), 7.77 (s, 1H), 7.23 - 7.17 (m, 4H), 7.02 (tt, J = 4.5, 2.3 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 4.18 (dd, J = 6.0, 4.7 Hz, 1H), 3.24 (q, J = 6.8 Hz, 2H), 2.67 (t, J = 7.3 Hz, 2H), 2.54 - 2.33 (m, 2H).

APCI-MS m/z: 372.3 [MH^+]

Example 124

N-(2-Biphenyl-4-yl-2-hydroxy-ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

a) 4-Phenylphenyloxirane

4-Phenyl-(α-bromoacetophenone), 8.25 g (0.030 mol), was slurried in methanol (150 mL). Sodium borohydride (3.80 g; 0.10 mol) was added in portions to give an exothermal reaction and a homogeneous reaction mixture. After 20 hours, water (600 mL) was added and the mixture was extracted with dichloromethane (500 mL). The organic phase was evaporated to give 7.25 g of crude product. NMR analysis showed mainly a 1:1 mixture of epoxide and vicinal bromo alcohol.

b) 2-Amino-1-biphenyl-4-yl-ethanol

The product mixture obtained in a) above was dissolved in THF (ca 100 mL) and a large excess of concentrated ammonia and ethanol was added to give a homogeneous system. TLC analysis after 4 hours showed only starting materials. A slight increase in temperature gave scarce improvement and the mixture was finally heated to 70° C in a sealed vessel for 20 hours. TLC analysis showed absence of starting materials and NMR analysis showec a complex mixture of products. The solvents were evaporated and dichloromethane (150 mL) was added to give a precipitate. The mixture was filtered and the solid, about 3.8 g, and filtrate was analysed with TLC and NMR. Analyses showed mixtures of products but with, possibly, expected product in the solid phase. A sample of

the solid (1.04 g) was purified by silica gel chromatography (200 mL) using dichloromethane/ methanol/ concentrated ammonia (90 +10+1) as eluant. Evaporation of pure fractions gave 0.62 g of the sub-titled compound.

c) N-(2-Biphenyl-4-yl-2-hydroxy-ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

The title compound was prepared by a method analogous to that described in Example 42e).

^{1}H NMR (400MHz,DMSO-d_6): δ 10.57 (s, 1H), 8.10 (q, J = 5.8 Hz, 1H), 7.79 (s, 1H), 7.64 (t, J = 8.5 Hz, 4H), 7.45 (q, J = 7.7 Hz, 4H), 7.35 (t, J = 7.3 Hz, 1H), 5.49 (s, 1H), 4.66 (t, J = 3.7 Hz, 1H), 4.26 - 4.17 (m, 1H), 3.20 - 3.09 (m, 1H), 2.59 (dt, J = 15.5, 3.5 Hz, 1H), 2.52 - 2.39 (m, 2H).

APCI-MS m/z: 336.3 [MH$^+$]

<u>Example 125</u>

N-[2-(1,1'-Biphenyl-4-yl)-2-methoxyethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

a) 4-(2-Amino-1-methoxyethyl)-biphenyl

4-Vinyl-biphenyl, 1.70 g (9.4 mmol), was dissolved in methanol (10 mL) and dichloromethane (15 mL). Bromine, 0.48 mL (9.4 mmol), dissolved in methanol (10 mL) was added over 30 minutes and TLC analysis showed complete reaction. The mixture was diluted with dichloromethane and added to an aqueous solution of sodium hydrogen sulphite and the mixture was shaken. The dichloromethane phase was washed with aqueous sodium hydrogen carbonate and water and evaporated to give 2.81g product. The product was purified by silica gel chromatography silica gel (200 mL) with heptane/ ethyl acetate (95 + 5) to give 1.00 g (39 %) of pure 4-(2-bromo-1-methoxy-ethyl)-biphenyl.

4-(2-Bromo-1-methoxyethyl)-biphenyl, 1.00 g (3.64 mmol), was dissolved in ethanol (20 mL) and added to a large excess of concentrated ammonia (20 mL). The mixture was heated to 100° C in a sealed vessel for 16 hours and evaporated. Chromatography on silica

gel (180 mL) with dichloromethane followed by dichloromethane/ methanol/ concentrated ammonia (90 + 10 + 1) gave 0.47 g (61 %) of the sub-titled compound.

b) N-[2-(1,1'-Biphenyl-4-yl)-2-methoxyethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

The title compound was prepared by a method analogous to that described in Example 42e).

^{1}H NMR (400MHz,DMSO-d_6): δ 10.56 (s, 1H), 8.16 (d, J = 5.5 Hz, 1H), 7.78 (d, J = 6.2 Hz, 1H), 7.70 - 7.64 (m, 4H), 7.47 (t, J = 7.6 Hz, 2H), 7.42 - 7.34 (m, 3H), 4.29 (dt, J = 7.8, 5.0 Hz, 1H), 4.23 - 4.19 (m, 1H), 3.19 (s, 3H), 2.61 - 2.53 (m, 2H), 2.50 - 2.39 (m, 2H).

APCI-MS m/z: 368.2 [MH$^+$]

__Example 126__

N-[2-(1,1'-Biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-N-methylacetamide

a) (4-Phenylphenethyl)-N-methylamine

4-Phenylphenethyl amine, 0.48 g (2.4 mmol), was added to an excess of methyl formate (5 mL) and dichloromethane (5 mL) was added to improve solubility. The heterogeneous reaction mixture was refluxed to give a solution within 20 hours. NMR analysis of a sample showed almost complete conversion to N-formyl amine. The reaction mixture was evaporated to give 0.47 g (87%). The formyl compound, 0.47 g (2.09 mmol), was dissolved in THF and 2.1 mL of 1.0 M lithium aluminium hydride (2.1 mmol) in THF was added. TLC analysis after 20 hours showed only starting material and 2 mL (2 mmol) of lithium aluminium hydride solution was added. Analysis after 1 hour showed starting material and the mixture was heated to reflux. After 1.5 hours a precipitate was formed, the starting material consumed and tetrahydrofuran (15 ml) was added. The mixture was quenched by successive addition of water (0.15 g), 15 % aqueous sodium hydroxide (0.15 g) and water (0.45 g). The mixture was filtered and evaporated to give 0.33 g crude

product. The crude product was purified by silica gel chromatography (100 mL) using dichloromethane/ methanol/ concentrated ammonia (90 + 10 + 1) as eluant. Evaporation of pure fractions gave 78 mg (18 %) of the sub-titled compound.

b) N-[2-(1,1'-Biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-N-methylacetamide

The title compound was prepared by a method analogous to that described in Example 42e).

APCI-MS m/z: 352.3 [MH^+]

__Example 127__

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-phenylethynyl-piperidin-1-yl)ethyl]-acetamide

a) 4-(Phenylethynyl)piperidine

N-BOC-4-ethynylpiperidin, 0.5 g (2.40 mmol), and iodobenzene, 0.29 mL (2.64 mmol) were dissolved in triethylamine (9 mL) and argon was passed through for a few minutes. Copper(I) iodide, 0.087 g (0.5 mmol), and bis[triphenylphosphine]palladium dichloride, 0.070 g (0.1 mmol), were added and the mixture was heated to 82°C in a closed vessel for 17 hours. TLC analysis indicated complete reaction. Triethylamine was evaporated and the mixture was purified by silica gel chromatography (75 mL) using heptane/ethyl acetate (4 + 1) as eluant. Evaporation of pure fractions gave 0.497 g (73 %) of N-BOC-4-(phenylethynyl)piperidine. The protected piperidine, 0.497 g (1.74 mmol), was dissolved in dichloromethane and trifluoroacetic acid (1 mL) was added. The reaction was completed within 20 hours and the mixture was evaporated to give an oil. NMR analysis showed pure ammonium trifluoroacetate, contaminated with trifluoroacetic acid. The product was dissolved in dichloromethane and extracted with aqueous sodium hydrogen carbonate and water. Evaporation of solvent gave 0.284 g (88 %) of the sub-titled compound.

b) 2-[4-(Phenylethynyl)piperidin-1-yl]ethanamine

4-(Phenylethynyl)piperidine (0.5 mmol, 92mg) was dissolved in acetonitrile (anhydrous 4Å, 4mL) together with bromoethylphtalimide (0.5mmol, 128mg) and K_2CO_3 (2mmol, 276mg). The reaction mixture was heated to reflux for 3hours, diluted with ethyl acetate (50mL) and washed with HCl/aq (1M, 50mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness. The protection group was removed by stirring the compound in methylamine (33% in ethanol, 5mL) for another 3 hours. The mixture was evaporated, diluted with ethyl acetate (50mL) and washed with NaOH (1M, 50mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was used without further purification.

c) 2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-phenylethynyl-piperidin-1-yl)ethyl]-acetamide

The title compound was prepared by a method analogous to that described in Example 42e).

^{1}H NMR (400MHz,$CDCl_3$): δ 9.96 (s, 1H), 9.67 (s, 1H), 8.23 (s, 1H), 7.34 (dd, J = 66.3, 28.1 Hz, 5H), 4.35 (s, 1H), 3.82 - 1.88 (m, 15H).

APCI-MS m/z: 369.3 [MH^+]

__Example 128__

***N*-{2-[(4-Bromobenzyl)oxy]ethyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide**

a) 2-(4-Bromo-benzyloxy)-ethylamine hydrochloride

Sodium hydride (60 % in oil, 0.613 g, 15 mmol) was added in small portions over 5 minutes to a solution of tert-butyl N-(2-hydroxyethyl)-carbamate (1.771 g, 10.99 mmol), 4-bromobenzylbromide (2.676 g, 10.708 mmol) in dimethyl formamide (50 ml). The mixture was stirred for 2 hours at ambient temperature under argon. The mixture was partitioned between water (250 mL), ethyl acetate (50 mL) and heptane (50 mL). The organic phase was washed two times with water (30 mL). Evaporation afforded 3.13g of a

clear oil. The oil was stirred in 2.5 M HCl in ethyl acetate (50 mL) for 2 hours. Filtering and washing with ethyl acetate afforded the sub-titled compound (2.256 g, 98.1 % yield).
^{1}HNMR (300 MHz, DMSO-d_6): δ 8.16 (3H, bs); 7.55 (2H, d); 7.36 (2H, d); 4.51 (2H, s); 3.64 (2H, t); 2.99 (2H, t).
APCI-MS m/z: 229.9; 231.9 [MH^+]

b) *N*-{2-[(4-bromobenzyl)oxy]ethyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

The title compound was prepared by a method analogous to that described in Example 42e).
^{1}HNMR (300 MHz, DMSO-d_6): δ 10.56 (1H, s); 8.08 (1H, t); 7.81 (1H, s); 7.54 (1H, d); 7.30 (1H, d); 4.45 (2H, s); 4.20 (1H, m); 3.25 (2H, q); 2.50 (2H, p); 2.50 (2H, m).
APCI-MS m/z: 370; 372 [MH^+]

Example 129

2-(1,1'-Biphenyl-4-yl)-2-oxoethyl (2,5-dioxoimidazolidin-4-yl)acetate

Hydantoin acetic acid (109 mg, 0.69 mmol), 2-bromo-4'-phenylacetophenone (191 mg, 0.69 mmol) and N-ethyl-diisopropylamine (120 μl, 0.70 mmol) were stirred in dimethylformamide (5.0 mL) at 50°C for 3 hours. Evaporation and chromatography on silica (dichloromethane/methanol: 100/3) afforded 123 mg of the title compound in 50.1 % yield.
^{1}HNMR (300 MHz, DMSO-d_6): δ 10.68 (1H, s); 8.06 (2H, d); 7.90 (1H, s); 7.87 (2H, d); 7.77 (2H, d); 7.55-7.42 (3H, m); 5.55 (2H, d); 4.32 (1H, dt); 2.90 (2H, d).
APCI-MS m/z: 353.1 [MH^+]

Pharmacological Example

Isolated Enzyme Assay

Recombinant human MMP12 catalytic domain may be expressed and purified as described by Parkar A.A. *et al*, (2000), Protein Expression and Purification, 20:152. The purified

enzyme can be used to monitor inhibitors of activity as follows: MMP12 (50 ng/ml final concentration) is incubated for 60 minutes at room temperature with the synthetic substrate Mac-Pro-Cha-Gly-Nva-His-Ala-Dpa-NH_2 in assay buffer (0.1M "Tris-HCl" (trade mark) buffer, pH 7.3 containing 0.1M NaCl, 20mM $CaCl_2$, 0.020 mM ZnCl and 0.05% (w/v) "Brij 35" (trade mark) detergent) in the presence (5 concentrations) or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 320nm and λem 405nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$\text{Fluorescence}_{\textit{plus inhibitor}}$ - $\text{Fluorescence}_{\textit{background}}$] divided by the [$\text{Fluorescence}_{\textit{minus inhibitor}}$ - $\text{Fluorescence}_{\textit{background}}$].

For example, the following table shows the IC_{50} figures for a representative selection of compounds according to the invention when tested in the MMP12 enzyme assay.

Compound of Example No.	Human MMP12 IC_{50} (μm)
1	0.022
2	0.007
5	0.032
14	0.006
21	0.008
22	0.015
23	0.006
24	0.004
26	0.017
27	0.005